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REVIEW

Cervical Lymph Node Metastasis in Adenoid Cystic Carcinoma of the Larynx: A Collective International Review

Andrés Coca-Pelaz · Leon Barnes · Alessandra Rinaldo · Antonio Cardesa · Jatin P. Shah · Juan P. Rodrigo · Carlos Suárez · Jean Anderson Eloy · Justin A. Bishop · Kenneth O. Devaney · Lester D. R. Thompson · Bruce M. Wenig · Primož Strojan · Marc Hamoir · Patrick J. Bradley · Douglas R. Gnepp · Carl E. Silver · Pieter J. Slootweg · Asterios Triantafyllou · Vincent Vander Poorten · Michelle D. Williams · Alena Skálová · Henrik Hellquist · Afshin Teymoortash · Jesus E. Medina · K. Thomas Robbins · Karen T. Pitman · Luiz P. Kowalski · Remco de Bree · William M. Mendenhall · Robert P. Takes · Alfio Ferlito

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ABSTRACT

Adenoid cystic carcinoma (AdCC) of the head and neck is a well-recognized pathologic entity that rarely occurs in the larynx. Although the 5-year locoregional control rates are high,

distant metastasis has a tendency to appear more than 5 years post treatment. Because AdCC of the larynx is uncommon, it is difficult to standardize a treatment protocol. One of the controversial points is the decision whether or not to perform an elective neck dissection on these patients. Because there is contradictory information about this issue, we have critically reviewed the literature from 1912 to 2015 on all reported cases of AdCC of the larynx in order to clarify this issue. During the most recent period of our review (1991–2015) with a more exact diagnosis of the tumor

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A. Coca-Pelaz · J. P. Rodrigo
Department of Otolaryngology, Hospital
Universitario Central de Asturias, Oviedo, Spain

L. Barnes
Department of Pathology, University of Pittsburgh
School of Medicine, Pittsburgh, PA, USA

A. Rinaldo
University of Udine School of Medicine, Udine, Italy

A. Cardesa
Department of Anatomic Pathology, Hospital
Clínic, University of Barcelona, Barcelona, Spain

J. P. Shah
Head and Neck Surgery, Memorial Sloan Kettering
Cancer Center, New York, NY, USA

J. P. Rodrigo · C. Suárez
Instituto Universitario de Oncología del Principado
de Asturias, University of Oviedo, Oviedo, Spain

C. Suárez
Fundación de Investigación e Innovación
Biosanitaria del Principado de Asturias, Oviedo,
Spain

J. A. Eloy
Department of Otolaryngology-Head and Neck
Surgery, Neurological Institute of New Jersey,
Rutgers New Jersey Medical School, Newark, NJ, USA

J. A. Bishop
Departments of Pathology and
Otolaryngology-Head and Neck Surgery, The Johns
Hopkins Medical Institutions, Baltimore, MD, USA

histology, 142 cases were observed of AdCC of the larynx, of which 91 patients had data pertaining to lymph node status. Eleven of the 91 patients (12.1%) had nodal metastasis and, based on this low proportion of patients, routine elective neck dissection is therefore not recommended.

Keywords: Adenoid cystic carcinoma; Clinical protocols; Elective neck dissection; Larynx; Lymph node metastasis; Neck; Oncology; Treatment

INTRODUCTION

Adenoid cystic carcinoma (AdCC) is an uncommon tumor, accounting for about 1% of all head and neck malignancies [1]. It is typically a slowly growing but relentlessly progressive neoplasm characterized by

perineural invasion, frequent local recurrences and late distant hematogenous dissemination to the lung, liver, bone and brain. In contrast lymph node metastasis, especially true embolic lymph node metastasis, is infrequent. Although the long term prognosis is poor, some patients may survive 10–15 years or more before succumbing to their disease.

In a recent international collaborative study involving nine cancer centers worldwide Amit et al. identified 270 patients with AdCC of the head and neck who underwent neck dissection and observed the overall incidence of neck metastasis to be 29% [2]. In the same year they also observed a 17% incidence of occult nodal metastasis among those patients who underwent elective neck dissections [3]. Because of its rarity, it is uncertain whether their data regarding the frequency of lymph node metastasis might also apply to AdCC of the larynx. To address this issue we critically

K. O. Devaney
Department of Pathology, Allegiance Health,
Jackson, MI, USA

L. D. R. Thompson
Southern California Permanente Medical Group,
Woodland Hills, CA, USA

B. M. Wenig
Department of Pathology, Beth Israel Medical
Center, New York, NY, USA

P. Stojan
Department of Radiation Oncology, Institute of
Oncology, Ljubljana, Slovenia

M. Hamoir
Department of Head and Neck Surgery, Head and
Neck Oncology Program, St Luc University Hospital
and King Albert II Cancer Institute, Brussels,
Belgium

P. J. Bradley
Department of Otolaryngology-Head and Neck
Surgery, Nottingham University Hospitals, Queens
Medical Centre Campus, Nottingham, UK

P. J. Bradley · V. Vander Poorten
European Salivary Gland Society, Geneva,
Switzerland

D. R. Gnepp
University Pathologists, Providence, RI, USA

D. R. Gnepp
University Pathologists, Fall River, MA, USA

C. E. Silver
Departments of Surgery and Otolaryngology – Head
and Neck Surgery, Albert Einstein College of
Medicine, Montefiore Medical Center, Bronx, NY,
USA

P. J. Slootweg
Department of Pathology, Radboud University
Medical Center, Nijmegen, The Netherlands

A. Triantafyllou
Oral and Maxillofacial Pathology, School of
Dentistry, University of Liverpool and Cellular
Pathology, Liverpool Clinical Laboratories,
Liverpool, UK

V. Vander Poorten
Otorhinolaryngology-Head and Neck Surgery and
Department of Oncology, Section Head and Neck
Oncology, University Hospitals Leuven, KU Leuven,
Leuven, Belgium

reviewed the world literature on AdCC of the larynx in an attempt to suggest guidelines for the management of the neck in patients with AdCC at this anatomic site. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

REVIEW OF THE LITERATURE AND ANALYSIS

Minor salivary-type glands are present in most of the laryngeal mucosa: abundantly in the subglottis, false cords/anterior commissure and usually absent from the true cords [4]. Yet despite their presence, glandular neoplasms are distinctly unusual. AdCC is one of the most frequent. Because of their rarity, no single institution has accumulated a large series of cases, and therefore, only single case reports or small series are available for review,

which often results in widely conflicting data. Eschwege et al. [5] reported five cases of AdCC of the larynx and all were free of cervical lymph node metastasis as opposed to Spiro and Huvois [6] who also reported five cases and observed that four had associated positive lymph nodes (80%). Accordingly, to appreciate the potential biological behavior of AdCC of the larynx one often must rely on a composite review of published cases. However, this approach is also hampered by lack of quality data. Some cases are poorly documented with no histologic illustrations, and pertinent clinical and/or pathologic details are often not reported, including long term follow-up (more than 10 years). In addition, recent new histopathological entities have been described that may have been or continue to be confused with AdCC, such as basaloid squamous cell carcinoma, polymorphous low grade carcinoma, epithelial-myoepithelial carcinoma,

M. D. Williams
Department of Pathology, The University of Texas
MD Anderson Cancer Center, Houston, TX, USA

A. Skálová
Department of Pathology, Faculty of Medicine in
Plzen, Charles University in Prague, Plzen, Czech
Republic

H. Hellquist
Department of Biomedical Sciences and Medicine,
University of Algarve, Faro, Portugal

A. Teymoortash
Department of Otolaryngology-Head and Neck
Surgery, Philipp University, Marburg, Germany

J. E. Medina
Department of Otorhinolaryngology, The
University of Oklahoma Health Sciences Center,
Oklahoma City, OK, USA

K. T. Robbins
Division of Otolaryngology-Head and Neck Surgery,
Southern Illinois University School of Medicine,
Springfield, IL, USA

K. T. Pitman
Department of Surgery, Banner MD Anderson
Cancer Center, Gilbert, AZ, USA

L. P. Kowalski
Department of Head and Neck Surgery and
Otorhinolaryngology, A.C. Camargo Cancer Center,
São Paulo, Brazil

R. de Bree
Department of Head and Neck Surgical Oncology,
UMC Utrecht Cancer Center, University Medical
Center Utrecht, Utrecht, The Netherlands

W. M. Mendenhall
Department of Radiation Oncology, University of
Florida, Gainesville, FL, USA

R. P. Takes
Department of Otolaryngology-Head and Neck
Surgery, Radboud University Medical Center,
Nijmegen, The Netherlands

A. Ferlito (✉)
Coordinator of the International Head and Neck
Scientific Group, Padua, Italy
e-mail: a.ferlito@uniud.it

basal cell adenocarcinoma, and cribriform adenocarcinoma.

With these limitations in mind, we undertook a literature search of PubMed (including Medline) using the search strategy “adenoid cystic carcinoma larynx” and “adenoid cystic carcinoma head neck” which resulted in 1292 articles, which were hand-searched for pertinent articles. Their reference lists were also searched for additional cases. We excluded cases without a definitive diagnosis of AdCC, cases where the location of the tumor was not definitely the larynx and cases which were included in previously published reviews (as stated in the table, see remarks). As stated above only a few cases reported include a complete staging procedure, the extent of neck dissections, histology images illustrating the definitive diagnosis, why the authors performed a neck dissection, follow-up of the patient, recurrence of the lesion and location of the recurrence. Our comprehensive review of AdCC of the larynx reported in the literature from 1912 to 2015 includes 252 cases as shown in Table 1 [3, 5–110] (excluded cases have been summarized in Table 2). Based on these data, our review indicates that AdCC of the larynx occurs in individuals averaging 52.3 years of age (range 12–84 years) and is more common in males (60.7%). The most frequent site of origin is the subglottis (58.2%) followed by the supraglottis (32.1%) and glottis (9.7%). Of the 252 cases, the status of the regional lymph nodes was specifically mentioned in 156, and of these 24 (15.4%) were associated with cervical lymph node metastasis. Due to the lack of sufficiently long term follow-up, the number of 47 cases reported to have had distant metastasis is probably underestimated.

Of the 24 cases with lymph node metastasis, information about the specific location of the

tumor within the larynx was available in 16, and of these 9 arose in the supraglottis, 6 in the subglottis and 1 in the glottis.

Over the last century there have been advances in our understanding and classification of salivary tumors and new entities have been described some of which show histologic similarities to AdCC. Accordingly, one might question the authenticity of some of the cases labeled as AdCC of the larynx in the older literature. Considering the fact that basaloid squamous cell carcinoma was first described in 1986 [111], polymorphous low grade adenocarcinoma in 1983 [112], epithelial-myoepithelial carcinoma in 1972 [113], basal cell adenocarcinoma in 1988 [114] and cribriform adenocarcinoma in 1999 [115], all potential histologic mimickers of AdCC, we divided our review into two time periods, (a) 1912–1990 (we have further subdivided this into two time periods due to the description of epithelial-myoepithelial carcinoma in 1972) and (b) 1991–2015 (Table 3), in order to analyze whether the incidence of lymph node metastasis in AdCC of the larynx was higher before the description of these “new” tumors which may have been mistaken histologically for AdCC. Between 1912 and 1990, we identified 110 cases of AdCC of the larynx and, of these, 65 had data regarding lymph node status. Thirteen of these 65 patients (20%) had lymph node metastasis. For the period 1991–2015, 142 cases were observed and of these reports 91 patients had data pertaining to lymph node status. Eleven of the 91 patients (12.1%) had nodal metastasis. Possibly, this decline in the incidence of lymph node metastasis between the two time periods might in part be related as noted above to incorrect histological diagnosis prior to 1991, though the difference does not appear statistically significant ($\chi^2 = 1.75$, $df = 1$, $p > 0.05$).

Table 1 Review of reported cases of adenoid cystic carcinoma of the larynx

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Broeckaert (1912) [8]	1	57	M	SG	Absent	Absent	
Bourgeois and Soulas (1931) [9]	1	34	F	E	Absent	Present	Distant metastasis to lungs
Eigler (1932) [10]	1	45	F	E	Absent	Present	Distant metastasis to cervical spine
Lemaître et al. (1936) [11]	1	34	M	E	Absent	Absent	
Kramer and Som (1939) [12]	1	36	M	SuG	Absent	Absent	
Ide and Cahn (1948) [13]	1	52	M	SuG	Absent	Absent	
McDonald and Havens (1948) [14]	4	NA	NA	2 L 2 SuG	NA	NA	Data analyzed mixed with other locations and histologies
Pirodda (1951) [15]	1	NA	NA	L	NA	NA	
Berdal and Mylius (1954) [16]	1	36	F	SuG	Absent	Absent	
Purney and McStravog (1954) [17]	1	55	M	SG	Present	Absent	Lymph node involvement due to invasion of extensive recurrent tumor
Abercromby and Rewell (1955) [18]	1	NA	NA	L	NA	NA	
Ahued (1956) [19]	1	48	M	E	Present	Present	Cervical lymph node involvement due to direct invasion of the primary tumor
Murtagh and House (1956) [20]	1	40	M	L	Absent	Present	Distant metastasis to lungs, fifth rib, diaphragm, pleurae
							Distant metastasis to lungs

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Pierrantoni and Leonardelli (1957) [21]	2	42	F	L	Absent	Absent	
		49	F	L	Absent	Absent	
Soboroff (1959) [22]	1	60	F	SuG	Absent	Absent	
Leroux-Robert et al. (1961) [23]	7	58	M	Left AEF, PS	Absent	Absent	Some reservations about the correct identification of the oncotypes
		55	M	Right PS	Absent	Present	
		NA	M	Right HL	Absent	Absent	Patient 2 with distant metastasis to lungs
		NA	M	Right PS	Absent	Absent	
		53	M	E, left AEF	Absent	Absent	
		54	M	E	Absent	Absent	
		69	M	SuG	Absent	Absent	
Ash et al. (1964) [24]	1	29	M	Right VC, FVC, V, T	NA	NA	
Iosipescu and Manolescu (1965) [25]	1	72	M	G	Absent	Absent	
Rosenfeld et al. (1966) [26]	3	NA	NA	L	NA	NA	
		NA	NA	L	NA	NA	
		NA	NA	L	NA	NA	
Toomey (1967) [27]	1	68	F	SuG, T	Present	Absent	Bilateral cervical nodes
Cady et al. (1968) [28]	3	NA	NA	L	NA	NA	
		NA	NA	L	NA	NA	
		NA	NA	L	NA	NA	
Allachy (1969) [29]	1	58	F	SuG, Left L	Absent	Absent	
Berdal et al. (1969) [30]	1	36	F	SuG	Absent	Absent	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Leonardelli and Pizzetti (1970) [31]	4	38	M	SuG	Absent	Present	Metastatic spread
		39	M	SuG, Left VC	Absent	Absent	
		31	M	Left FVC and V	Absent	Absent	
		51	F	Left L	Absent	Absent	
Adams and Duvall (1971) [32]	1	NA	NA	Right FVC, AEF, E	Present	Present	Bilateral positive cervical nodes with histology illustration in text
Pincini and Mandelli (1971) [33]	1	53	M	SuG	Absent	Absent	
Jelínek (1973) [34]	1	NA	NA	SuG	NA	NA	
Spiro et al. (1973) [35]	3	NA	NA	2 SG, 1 G	NA	NA	
Ackerman and Rosai (1974) [36]	3	NA	NA	L	NA	NA	Lymph node involvement due to embolic metastasis or contiguous infiltration?
		NA	NA	L	NA	NA	
		NA	NA	L	Present	Present	Distant metastasis to lungs
Gross et al. (1974) [37]	1	NA	NA	VC, FVC	NA	NA	
Muzaffar and Bolstad (1974) [38]	1	47	F	L	NA	NA	
Whicker et al. (1974) [39]	9	NA	NA	NA	NA	NA	One case with lymph nodes due either to direct infiltration or classic embolic metastasis
Eschwege et al. (1975) [5]	5	46	M	L	Absent	Absent	Distant metastasis to lungs
		52	M	E	Absent	Absent	Distant metastasis to lungs; cancer of cervix associated
		53	M	VC, PLW	Absent	Present	
		66	F	SuG	Absent	Present	
		73	M	SuG	Absent	Absent	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Gerard and De Gandt (1975) [40]	1	71	F	SuG, G	Absent	Present	Distant metastasis to lungs
Sessions et al. (1975) [41]	3	NA	NA	NA	NA	NA	Clinical information are mixed with other glandular neoplasms
Houle et al. (1976) [42]	1	52	M	Right AEF, FVC, arytenoid and PS	Absent	Absent	20 lymph nodes histologically free
Kekelidze (1976) [43]	1	NA	NA	L	NA	NA	
Spiro et al. (1976) [44]	3	57	M	G	Present	Present	Carcinomatosis
		70	F	E	Absent	Absent	
		38	M	E	Absent	Absent	
Olofsson and van Nostrand (1977) [45]	4	26	F	SuG and T	Absent	Absent	Three paraesophageal positive nodes, not palpated; distant metastasis to lungs
		63	M	SuG, T, esophagus, pharynx, thyroid gland	Present	Present	
		66	F		Absent	Absent	
		56	M	Right L	Absent	Absent	
				SuG, left VC and FVC			
Fleischer et al. (1978) [46]	5	54	M	E, left AEF and PS	Absent	Absent	With histological illustration
		41	M	FVC	Present	Absent	Distant metastasis to lung and brain
		35	M	SuG	Absent	Present	
		63	F	SuG	NA	NA	
		52	M	SuG	Absent	Absent	
Mankodi and Shah (1979) [47]	1	72	M	SuG	Absent	Absent	
Marsh and Allen (1979) [48]	1	50	F	SuG	Absent	Present	Distant metastasis to lung

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Donovan and Conley (1983) [49]	3	42	F	SuG, T, esophagus, paratracheal area	Present	Present	Distant metastasis to lungs, liver
		70	F		Absent	Absent	Neck recurrence but not specified if it was on a lymph node
		58	F	SuG, T SuG, T	Absent	Absent	
Ferlito and Caruso (1983) [50]	2	52	F	E	Absent	Absent	
		29	F	SuG	Absent	Absent	
Tewfik et al. (1983) [7]	1	79	M	SuG	Absent	Absent	
Cohen et al. (1985) [51]	8	NA	NA	5 SG, 3 SuG	3 Present	NA	Two patients with lymph nodes at diagnosis, one patient manifested lymph nodes 13 years after diagnosis
Stullwaggon et al. (1985) [52]	1	55	M	E	Present	Present	AdCC-HGT
							Five cervical lymph nodes positive with extracapsular invasion (histological illustration)
							Distant metastasis to liver, bone marrow, lymph nodes, brain, heart, lungs and kidneys
Gadomski et al. (1986) [53]	2	68	M	SG	NA	Absent	The first patient underwent modified neck dissection but the results are not available in the text
		54	M	E	Present	Present	He is alive and free of disease
Jones et al. (1986) [54]	1	34	F	SuG	Absent	Absent	
Li (1988) [55]	7	NA	5 M/ 2F	3 SG, 3 G, 1 SuG	NA	NA	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Ferlito et al. (1990) [56]	6	52	F	SG	Absent	Absent	Distant metastasis to liver, bones
		29	F	SuG	Absent	Absent	One incidental node free of tumor
		72	F	SuG	Absent	Present	66 left cervical nodes free of tumor
		58	F	SuG	Absent	Absent	Positive resection margins; distant metastasis to lungs
		48	M	SuG	Absent	Absent	This series includes the two cases of AdCC reported previously by Ferlito and Caruso in 1983 [50]
		76	M	SG	Absent	Present	
Case 3 distant metastasis prior to treatment							
Paredes Osado et al. (1990) [57]	1	52	F	SuG, T	Absent	Absent	
Dueñas Parrilla et al. (1991) [58]	1	65	M	E	Absent	Absent	
Serafini et al. (1991) [59]	2	62	M	SuG	Absent	Absent	
		54	M	SuG	Absent	Absent	
Spiro and Huvos (1992) [6]	5	NA	NA	L	Present	NA	Incidence of cervical metastasis was reported as 60% which does not match with their data of 4 out of 5 positive lymph nodes = 80%
		NA	NA	L	Present	NA	The present series includes the cases reported previously by Spiro et al. [35] and Spiro et al. [44]
		NA	NA	L	Present	NA	
		NA	NA	L	Present	NA	
		NA	NA	L	Absent	NA	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Bignardi et al. (1993) [60]	2	65	F	SG	Absent	Absent	No neck dissection; no RT; 6 years follow-up
		76	F	SuG	Absent	Absent	No neck dissection; postop RT; 4 years follow-up
Gierek et al. (1994) [61]	2	NA	NA	SuG, T	Absent	Absent	
		NA	NA	SuG, T	Absent	Present	
Anderson et al. (1995) [62]	3	NA	NA	SG	NA	Absent	Data mixed with other location
		NA	NA	SG	NA	Absent	(hypopharynx) and other histologic types of tumors
		NA	NA	SuG	NA	Absent	
de Kerviler et al. (1995) [63]	1	52	M	AEF	Present	Present	Seven of the eight lymph nodes contained tumor, with ruptured capsule
							Bilateral cervical lymph nodes recurrence and lung metastasis
Scott and Glover (1995) [64]	1	66	F	SuG	Absent	Absent	
Lam and Yuen (1996) [65]	1	56	F	SuG	NA	NA	One case of AdCC among 451 cancers of the larynx
Parsons et al. (1996) [66]	2	NA	NA	NA			Two cases of laryngeal AdCC among 57 AdCC of the head and neck
		NA	NA	NA			Data were analyzed together with other locations and histological subtypes
Spiro (1997) [67]	5	NA	NA	NA	NA	3 Present	These data are not accounted at the end of the table because they are included in a previous article [6]

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Srivastava and Bathia (1997) [68]	1	30	M	SuG	Absent	Absent	
Alavi et al. (1999) [69]	5	NA	NA	G	NA	NA	Data of different glandular carcinomas are mixed
		NA	NA	SG	NA	NA	
		NA	NA	SuG	NA	NA	
		NA	NA	SuG	NA	NA	
		NA	NA	SuG	NA	NA	
Damborenea Tajada et al. (1999) [70]	1	NA	NA	NA	NA	NA	
Fordice et al. (1999) [71]	2	NA	NA	NA	NA	NA	Data of AdCC of different locations analyzed together
Hogg et al. (1999) [72]	1	72	M	SuG	Absent	Absent	Patient with a goiter that confounded the diagnostic process
Morais Pérez et al. (1999) [73]	1	26	F	SG	Absent	Absent	No neck dissection
Veivers et al. (2001) [74]	1	39	M	SuG, anterior commissure	Absent	Present	Distant metastasis to lungs
Javadi et al. (2002) [75]	1	12	M	SuG	Absent	Absent	
Mahlstedt et al. (2002) [76]	6	NA	NA	SG	1 patient was N1	Absent	It is not specified in the article which patient was N1
		NA	NA	SG		Absent	Two patients underwent neck dissection
		NA	NA	SG		Absent	
		NA	NA	SG		Absent	
		NA	NA	SG		Absent	
		NA	NA	SuG		Absent	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Lee et al. (2003) [77]	1	50	M	E	Absent	Absent	
Silverman et al. (2004) [78]	4	NA	NA	NA	NA	NA	Data analyzed mixed with other locations
Gaissert et al. (2005) [79]	9	NA	NA	9 SuG	Absent	3 present	Three patients with AdCC died of distant disease
Garly et al. (2006) [80]	10	45	F	Arytenoid	Present	Present	AdCC-HGT
		40	F	E	Absent	Present	AdCC-HGT
		54	M	E	Absent	Absent	AdCC-HGT
		56	M	SuG	Absent	Absent	AdCC-HGT
		69	F	SuG	Absent	Absent	Distant metastasis to lungs and in patient 2 to lungs and bone
		74	F	SuG	Absent	Present	(Grade classification following the M. D. Anderson Grading [81])
		40	F	SuG	Present	Absent	
		53	M	SuG	Absent	Absent	
		54	M	SuG	Absent	Absent	
		55	M	SuG	Absent	Present	
Haddad et al. (2006) [82]	1	41	M	SuG, G	Absent	Absent	
Khan et al. (2006) [83]	1	30	F	SuG	Absent	Absent	
Wang et al. (2006) [84]	4	48	M	G	Absent	Absent	Dead without disease
		60	M	G	Absent	Absent	Dead without disease
		69	M	SG	Absent	Absent	Alive without disease
		58	M	SuG, G	Absent	Present	Dead of lung metastasis
Del Negro et al. (2007) [85]	1	55	F	SuG	Absent	Absent	
Messaoudi et al. (2007) [86]	1	49	M	SuG	Absent	Absent	
Aydin et al. (2008) [87]	1	16	F	SuG	Absent	Absent	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Moukarbel et al. (2008) [88]	15	NA	NA	NA	Absent	Present	No data available about lymph node status
		NA	NA	NA	Absent	Present	
		NA	NA	NA	Absent	Present	Two patients suffered regional recurrences, but without specifications (showed in the table as NA in lymph node column)
		NA	NA	NA	Absent	Absent	
		NA	NA	NA	Absent	Present	
		NA	NA	NA	Absent	Absent	
		NA	NA	NA	Absent	Absent	
		NA	NA	NA	Absent	Present	
		NA	NA	NA	Absent	Present	
		NA	NA	NA	Absent	Present	
		NA	NA	NA	Absent	Present	
		NA	NA	NA	NA	Absent	
		NA	NA	NA	Absent	Absent	
		NA	NA	NA	Absent	Present	
		NA	NA	NA	NA	Present	
Wang et al. (2009) [89]	1	54	F	SuG	Absent	Absent	
		55	M	SuG	Absent	Absent	
Zvrko and Golubović (2009) [90]	1						
Murray et al. (2010) [91]	1	26	M	L	NA	Present	Distant metastasis to lung and spleen
Nhembe et al. (2010) [92]	1	54	M	SuG	Absent	Absent	
Oplatek et al. (2010) [93]	5	NA	NA	NA	NA	NA	Data analyzed mixed with other locations
Zald et al. (2010) [94]	1	60	M	SuG, VC	Absent	Absent	
Lloyd et al. (2011) [95]	26	NA	NA	NA	NA	NA	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Balamucki et al. (2012) [96]	2	NA	NA	NA	NA	NA	Data were analyzed mixed with other locations
Boland et al. (2012) [97]	1	60	F	L	NA	NA	Dead of disease
Calzada et al. (2012) [98]	6	NA	NA	L	Absent	Absent	One of these patients had a modified
		NA	NA	Right AEF	Absent	Absent	radical neck dissection because of
		NA	NA	Right VC	Absent	Absent	palpable nodal disease (although
		NA	NA	Right VC	Absent	Present	final pathology showed no evidence
		NA	NA	SuG	Absent	Absent	of metastatic AdCC)
		NA	NA	SuG	Absent	Absent	
Costa et al. (2012) [99]	1	58	F	L	Absent	Present	
Friedman et al. (2012) [100]	1	NA	NA	SuG	Absent	Absent	
Nielsen et al. (2012) [101]	4	67	M	SG	Absent	NA	
		46	M	SuG	Absent	Absent	
		19	M	G	Absent	Absent	
		61	M	Transglottic	Absent	Absent	
Misiukiewicz et al. (2013) [102]	2	41	M	SuG	Absent	Present	Distant metastasis to lung
		73	M	G	Absent	Absent	
Testa et al. (2013) [103]	1	61	F	Left VC	Absent	Absent	Patient had bilateral cervical lymph node hyperplasia, but histological examination was free of metastasis

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
van Weert et al. (2013) [104]	3	NA	NA	3 L	Absent	Absent	Tumor site is referred as larynx/trachea
Qian et al. (2014) [105]	1	44	F	SG	Absent	Absent	Author by personal communication indicate us that there are four cases, three larynx and one trachea
Zhang et al. (2014) [106]	9	84	F	SuG	Absent	NA	
		36	M	SuG	Absent	NA	
		77	M	E, FVC	Absent	NA	
		75	M	AEF, FVC	Absent	NA	
		36	F	SuG	Absent	NA	
		48	M	SuG	Absent	NA	
		74	M	SuG	Present	NA	Seven patient dead of disease
		74	F	SuG, esophagus, mediastinum	Present	NA	
		70	M	V	Present	NA	
Amit et al. (2015) [3]	6	NA	NA	L	NA	NA	
					NA	NA	One case underwent neck dissection, but results are mixed with other locations
Carmel et al. (2015) [107]	1	NA	F	E, PS	Absent	Absent	Staging data were only available for 33 patients: 29 patients were N0, 1 N1, 2 N2 and 1 NX; 2 patients were M1 at the moment of diagnosis
Dubal et al. (2015) [108]	69	NA	NA	5 G, 26 SG, 31 SuG, 7 L	NA	NA	

Table 1 continued

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Hsu et al. (2015) [109]	1	NA	NA	L	NA	NA	
Liu and Chen (2015) [110]	6	46	M	SG	Absent	Present	Four patients underwent modified radical neck dissection because of palpable cervical lymph nodes
		61	M	SuG	Absent	Absent	
		56	F	SG	Absent	Present	All the lymph nodes had reactive hyperplasia without evidence of metastatic AdCC
		47	F	SuG	Absent	Absent	
		15	F	SuG	Absent	Absent	
		39	M	SuG	Absent	Absent	Patient 1 distant metastasis to lung, patient 3 to liver
Total Data Available	252	52.36	82M	96 SuG	24 ^a	47	Not counted: Spiro et al. [35, 44], Ferlito and Caruso [50], Spiro [67], Lloyd et al. [95], Dubal et al. [108]. See Table 2

AdCC adenoid cystic carcinoma, *AdCC-HGT* adenoid cystic carcinoma with high grade transformation, *AEF* aryepiglottic fold, *E* epiglottis, *F* female, *FVC* false vocal cord, *G* glottis, *HL* hemilarynx, *L* larynx, *M* male, *NA* not available, *PLW* pharyngolaryngeal wall, *PS* pyriform sinus, *RT* radiotherapy, *SG* supraglottis, *SuG* subglottis, *T* trachea, *V* ventricle, *V/C* vocal cord

^a Status of regional lymph nodes available in 156 cases

Table 2 Cases of AdCC of the larynx excluded in the analysis

Author (Year) [References]	No. cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis	Remarks
Spiro et al. (1973) [35]	3	NA	NA	2 SG, 1 G	NA	NA	Different salivary gland tumors analyzed by location or by histology These data are not accounted in Table 1 because they are included in a posterior article of the author [6]
Spiro et al. (1976) [44]	3	57	M	G	Present	Present	Carcinomatosis
		70	F	E	Absent	Absent	These data are not accounted in Table 1 because they are included in a posterior article of the author [6]
		38	M	E	Absent	Absent	
Ferlito and Caruso (1983) [50]	2	52	F	E	Absent	Absent	These data are not accounted in Table 1 because they are included in a posterior article of the author [56]
		29	F	SuG	Absent	Absent	
Spiro (1997) [67]	5	NA	NA	NA	NA	3 Present	These data are not accounted in Table 1 because they are included in a previous article of the author [6]
Lloyd et al. (2011) [95]	26	NA	NA	NA	NA	NA	These data are not accounted in Table 1 because it is not possible to know if they are previously published cases (SEER Database)
Dubal et al. (2015) [108]	69	NA	NA	5 G, 26 SG, 31 SuG, 7 L	NA	NA	Staging data were only available for 33 patients: 29 patients were N0, 1 N1, 2 N2 and 1 NX; two patients were M1 at the moment of diagnosis These data are not accounted in Table 1 because it is not possible to know if they are previously published cases (SEER Database)

Table 3 Cases of reported adenoid cystic carcinoma of the larynx according to different time periods

Period		No. of cases	Age	Sex	Location	Cervical lymph node metastasis	Distant metastasis
A	1912–1971	43	48.28	20M/10F	11 SG, 2 G, 13 SuG	3 Present ^a	7 Present
	1972–1990	67	55.44	23M/18F	17 SG, 6 G, 26 SuG	10 Present ^a	12 Present
B	1991–2015	142	52.50	39M/25F	25 SG, 8 G, 57 SuG	11 Present ^b	28 Present
A + B	1912–2015	252	52.36	82M/53F	53 SG, 16 G, 96 SuG	24 Present ^c	47 Present

G glottis, *SG* supraglottis, *SuG* subglottis

^a Status of regional lymph nodes available in 65 cases

^b Status of regional lymph nodes available in 91 cases

^c Status of regional lymph nodes available in 156 cases

DISCUSSION

Salivary gland carcinomas of the larynx are rare accounting for <1% of laryngeal malignancies [116] and it has already been noted that among these AdCC is one of the most common. Their rarity may be in part related to the paucity of accessory salivary (mucoserous) glands in this region [110]. It is reminded that the highest number of minor glands is localized in the subglottis; but they are also seen in the supraglottis and only infrequently in the glottis [80]. Moukarbel et al. [88], in a 40-year experience at the Princess Margaret Hospital of Toronto identified only 15 cases of AdCC of the larynx and observed the most frequent location to be the subglottis (60%). Others have also noted the predominant subglottic location of this tumor including Batsakis et al. [116] who found that 2 of their 3 tumors also arose in the subglottis as did 7 of the 10 tumors reported by Ganly et al. [80]. In our review of 252 cases of AdCC of the larynx, the exact location of the tumor was available in 165 and of these 58.2% arose in the subglottis, 32.1% in the supraglottis and 9.7% in the glottis.

AdCC has a distinct biological behavior as compared to other malignant tumors (slow

growth, propensity to neurovascular invasion, high frequency of distant metastasis and long-term survival with tumor) [96]. Another characteristic of AdCC is that lymph node metastases are infrequent with a reported overall incidence of approximately 10%, but this frequency may vary depending on the location of the lesion [e.g. base of tongue (19.2%), mobile tongue (17.6%), floor of mouth (15.3%)] [117], and up to half of the patients with nasopharyngeal AdCC [118]. In our review of 252 cases of AdCC of the larynx, information regarding the status of the regional lymph nodes was available in only 156 cases and of these only 24 tumors (15.4%) were associated with lymph node metastasis.

The finding of enlarged cervical lymph nodes in patients with AdCC of the larynx is however not uncommon. Liu and Chen [110] reviewed six cases of AdCC of the larynx four of which underwent modified radical neck dissection because of palpable cervical lymph nodes (cN+) and all four showed no evidence of metastasis on pathologic examination (pN–). Calzada et al. [98] identified, over a 30-year period, 11 patients with AdCC of the airway, six of which had tumors of the larynx. One of these patients underwent a modified radical neck

dissection due to palpable nodal disease, but the pathologic analysis of the neck dissection specimen reported only reactive lymph nodes. Testa et al. [103], also reported one case of a glottic-subglottic AdCC with bilateral cervical lymph node hyperplasia but with no evidence of metastasis. In a national study conducted in Denmark, Nielsen et al. [101] found four cases of AdCC of the larynx. All were staged N0, including the patient in whom a suspicious node was surgically removed.

In contrast, in 1977, Olofsson and van Nostrand [45] reported four cases of AdCC of the larynx and 1 of them had metastatic foci in three small paraesophageal lymph nodes. More recently, Dubal et al. [108] reviewed 69 cases of laryngeal AdCC of which 87.9% of the patients were N0. The remaining patients were staged N1 (one patient), N2 (two patients) and Nx (one patient) using the American Joint Committee on Cancer staging system. Amit et al. [2] in their international collaborative study of 270 patients who underwent neck dissection for AdCC, identified two cases of AdCC of the larynx, and one of them had positive lymph nodes. In a similar paper of Amit et al. [3] they reviewed the same series of 270 patients who underwent neck dissection for AdCC. This time, the authors identified six patients with AdCC of the larynx and only one of which underwent elective neck dissection. The definite pathologic result of this neck dissection is unknown because the results of all neck dissections were analyzed together.

Considering these data, the incidence of lymph node metastasis seems to be very low, with anecdotal cases reported. There are however several reports that contradict this view. Spiro and Huvos [6] reported five patients with AdCC of the larynx, 4 (80%) of which had associated lymph node metastasis.

TREATMENT SUGGESTIONS

Specific data on neck dissection in AdCC of the larynx are scarce. Therefore, we analyzed mainly the incidence of clinically overt lymph node metastasis in laryngeal AdCC. However, it can be anticipated that when this incidence is about 15.4% and the sensitivity of modern diagnostic techniques to detect occult lymph node metastasis is similar to that for head and neck squamous cell carcinoma, the rate of occult lymph node metastasis after current diagnostic work-up would be around 7%–8%, probably too low to warrant elective neck dissection in this group. Moreover, patients will be more at risk for distant than cervical lymph node metastasis.

Adenoid cystic carcinoma with high grade transformation (AdCC-HGT), however, is another issue that requires special attention. High-grade transformation (previously referred to as dedifferentiation) is defined as the abrupt transformation of a tumor into high-grade morphology that lacks the original distinct histologic characteristics [119]. These changes may be focal within the tumor and, as a result, AdCC-HGT may not always be appreciated pre-operatively. AdCC-HGT is an aggressive tumor with a high tendency to recur and metastasize to the lymph nodes (at least 50% or higher) and distant organs [120], as illustrated by the supraglottic tumor reported by Stillwagon et al. [52], which metastasized to five cervical lymph nodes with extracapsular extension, as well as to the liver, bone marrow, brain, heart, lungs and kidneys. AdCC-HGT must therefore be treated aggressively with due consideration for neck dissection.

The best treatment of the “conventional” laryngeal AdCC remains controversial. Standard treatment recommends a surgical approach

with or without postoperative radiotherapy. Liu and Chen [110] reported six cases of laryngeal AdCC, all of which were treated with surgical resection and postoperative radiotherapy. They reported no local recurrences and only two patients had distant metastasis (lung and liver) with a maximum follow-up of 6 years. With respect to cervical nodes, they did not recommend neck dissection in the absence of palpable lymph nodes (elective neck dissection), considering that four cases with palpable lymph nodes (cN+) were all free of tumor on histologic evaluation (pN–). Postoperative radiotherapy was recommended in view of the submucosal and perineural pattern of spread of this tumor. This explains why partial procedures or even total laryngectomy in AdCC may result in positive margins. For example, Moukarbel et al. [88] only achieved tumor free margins in 5 of 15 patients. In three patients results were not available and seven had positive margins. Only three patients suffered local recurrence. In contrast, Calzada et al. [98] achieved tumor free surgical margins in 5 of 6 patients (the sixth patient's margin status was unavailable) including two patients who underwent partial surgery. All the patients received postoperative external beam radiotherapy. No cases of local recurrence were documented and only one patient had a distant failure.

In view of these data, neck dissection seems to be an overtreatment in patients with AdCC of the larynx. The reasons for not performing neck dissection are: very low incidence of cervical lymph node metastasis (probably under 15.4%), low probability of neck recurrence (published cases with lymph node recurrences are anecdotal), need of complementary radiotherapy after the surgery due to the pattern of spread of this tumor (submucosal and perineural) and the low possibility of

undiagnosed positive lymph nodes. The reasons against not performing neck dissection are: the option of performing a neck dissection with a very low morbidity during the “open” surgery for the primary tumor and the observation that the appearance of enlarged lymph nodes in patients with AdCC is not uncommon, raising doubts to the surgeon about the correct diagnosis or the correct treatment.

LIMITATIONS

After commenting on this information, we would like to point out several limitations of this review: first of all, we have tried to be extremely accurate reviewing the cases published and we have tried to include “all” the cases from the literature. We appreciate that in the first period assessed (1912–1990) several cases with inexact histologic diagnosis could be found, but in order to be comprehensive, they were included in this review. There are a lot of cases with relevant information missing, but we had to include the data given by the authors although some of them did not give information about T stage, histologic grading, node levels involved, etc. As we have stated above the majority of the articles are case reports, and there are a lot of review articles mixing the data of AdCC of different locations in the head and neck.

CONCLUSION

Based on a thorough literature review, lymph node metastases in AdCC of the larynx are infrequent. In general, elective treatment of the neck is recommended for patients with squamous cell carcinoma of the upper aerodigestive tract when the anticipated risk of

occult metastasis is greater than 20%, based on a widely quoted decision analysis model like that proposed by Weiss et al. [121]. According to this, for the most recent period 1991–2015, with a more precise diagnosis of the tumor, 142 cases were observed of AdCC of the larynx and between them 91 patients had data pertaining to lymph node status. Only eleven of the 91 patients (12.1%) had nodal metastasis and in the previous period investigated (1912–1990) the incidence was also less than 20%. Therefore we think that elective neck dissection is not indicated, particularly if the neck is carefully examined by ultrasound and ultrasound-guided fine-needle aspiration biopsy in diagnostic work-up and follow-up.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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